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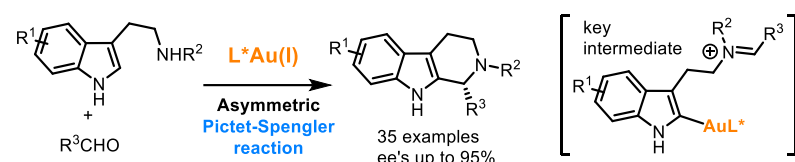
The Enantioselective Gold-Catalyzed Pictet-Spengler Reaction

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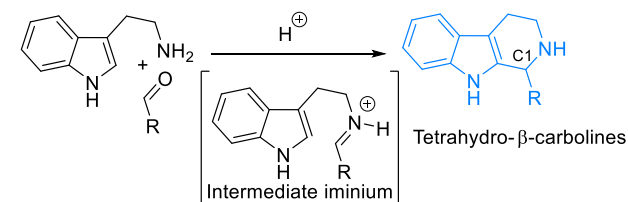


Supporting Information Placeholder

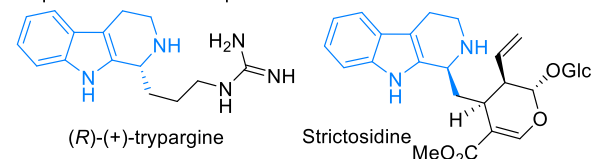
ABSTRACT: Cationic chiral Au(I)-complexes catalyze asymmetric Pictet-Spengler reactions between tryptamines and arylaldehydes. The resulting tetrahydro- β -carboline derivatives are obtained with wide functional group tolerance in high yields and ee's (up to 95%). Aldehydes bearing polar and/or protic functions are well tolerated. The reaction features a hitherto unknown C2-auration of the indole as the key step, supported by both kinetic isotope effect (KIE) measurement and DFT calculations.

The Pictet-Spengler reaction is the acid-catalyzed condensation of β -arylethylamines with aldehydes, leading to tetrahydroisoquinolines,¹ or tetrahydro- β -carboline (TH- β -Cs)² through the intermediacy of an iminium. With more than a century of intense research, the Pictet-Spengler reaction has now won its spurs as one of the most efficient and reliable methods for the synthesis of tetrahydro- β -carboline, a major class of heterocyclic compounds (Scheme 1).³ Some of these derivatives are natural products, such as (*R*)-tryptargine or strictosidine. Numerous compounds embedding this structural unit are endowed with wide and interesting biological activities and are currently available as drugs or drug candidates.^{3b}

Scheme 1. Structure and Natural Occurrence of Tetrahydro- β -Carbolines



Representative natural products

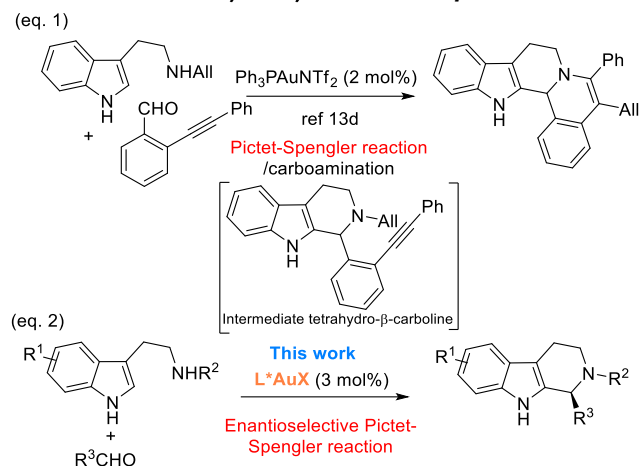


Numerous efforts have been made by synthetic chemists to control the absolute stereochemistry of C1.⁴ Enantioselective approaches to tetrahydro- β -carboline include the reduction of dihydro- β -carboline, using Ru or Rh chiral complexes via asymmetric transfer hydrogenation reactions⁵ or biocatalyzed reductions.⁶ However, the Pictet-Spengler re-

action is unarguably the leading synthetic strategy for the efficient synthesis of chiral tetrahydro- β -carboline.⁷ Beyond diastereoselective Pictet-Spengler reactions, enantioselective variants of the reaction can be catalyzed by Pictet-Spenglerase enzymes,⁸ or by Brønsted acid organocatalysis.⁹ Jacobsen, Seidel, List or Hiemstra have developed elegant enantioselective Pictet-Spengler reactions using chiral thioureas¹⁰ or chiral phosphoric acids¹¹ as catalysts, that have found numerous applications in total synthesis.^{11d, 12} Each of these methods has their strengths and weaknesses, either in the nature of the aldehyde used, the substituting pattern of the tryptamine or the electronic environment around the indole ring. However, in the context of such an important synthetic transformation, one must note that no enantioselective strategies using organometallic catalysis have been reported.

In the course of a project aiming at the synthesis of polycyclic indole derivatives,¹³ we used extensively the chiral phosphoric acid catalyzed Pictet-Spengler reaction to prepare key tetrahydro- β -carboline moieties that were cyclized to more complex polycyclic compounds using palladium.^{13a, 13b} or gold-catalysis.^{13c, 13d} During the study of the carboamination of *N*-allyltetrahydro- β -carboline to alkynes, we incidentally identified Au(I) complexes as efficient catalysts for the Pictet-Spengler reaction and developed a sequence combining this step with the carboamination cyclization (Scheme 2, eq. 1).^{13d} Precedence in the field was shown using achiral Au(I)¹⁴ or Au(III)¹⁵ complexes but it was however not clear from the literature the role that gold complexes could play in such a reaction, traditionally catalyzed by acids. In this paper, we demonstrate that chiral Au(I) complexes efficiently catalyze enantioselective Pictet-Spengler reactions (Scheme 2, eq. 2) and report our efforts in determining the scope of the reaction and understanding its mechanism.

Scheme 2. Gold-Catalyzed Synthesis of TH- β -Cs

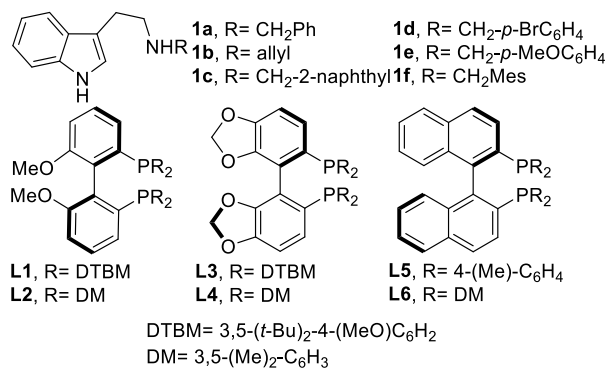


We initiated this work by establishing a suitable catalytic system. After we checked that tryptamine itself did not react in these conditions,¹⁶ we prepared a series of tryptamines **1** with diverse substituents to test under different catalytic conditions. We first engaged *N*-benzyl tryptamine **1a** in a Pictet-Spengler reaction with benzaldehyde **2a** in the presence of the Gagos' catalyst $Ph_3PAuNTf_2$ ⁴⁷ in DCM and molecular sieves,¹⁸ leading to the expected product **3aa** in 90% yield (Table 1, Entry 1). By anticipation that the use of chiral neutral Au(I) complexes necessitates a silver activation, we checked that the silver salt $AgNTf_2$ was not catalytically active (Entry 2). We next selected the DTBM-MeO-BIPHEP chiral ligand providing the digold complex $L_1(AuCl)_2$ (3 mol%), using $AgNTf_2$ (5.8 mol%) as chloride abstractor and screened tryptamines **1a-f** (Entries 3-8). Tryptamines **1b** and **1c** bearing an allyl and a naphthylmethyl group led to moderate enantiomeric excesses (Entries 4 and 5), while all other tryptamines substituted by a benzyl-type protecting group led to an average 75% ee in good yields (Entries 3, 6-8). The best enantiomeric excess was obtained with a CH_2Mes group, leading to 83% ee (Entry 8). We further screened a series of chiral diphosphines (Entries 9-13),¹⁹ that identified (DM)-SEGPHOS L_4 as the best chiral ligand, delivering a 93% ee (Entry 11).²⁰

The optimal conditions were then applied to a series of aromatic aldehydes using $L_4(AuCl)_2$ as the precatalyst and **1f** as the tryptamine partner on a 0.3 mmol scale (Scheme 3). Benzaldehyde afforded **3fa** in 97% yield and 92% ee. Aldehydes bearing a substituent in the *para* position led to excellent results with a good tolerance towards halide, alkyl and aryl substituents (**3fb** to **3ff**). Suitable crystals of compound **3fe** allowed to determine the absolute configuration of the stereogenic center as *R*.²¹ The presence of an electron-donating group led to a drop of the ee to 73% in **3fg**. Aldehyde **2h**, including a boronic acid function, led to **1fh** in 88% ee. The reaction performed from terephthalaldehyde **2i** led to **3fi** in an excellent 95% ee and 86% yield. Remarkably, there was no trace of difunctionalization in spite of the presence of a second aldehyde function. Finally, against all odds, the reaction tolerated the highly electrophilic nitro function, reputed reactive towards Au(I) complexes.²² The corresponding tetrahydro- β -carboline **3fj** was isolated in an excellent yield and with 72% ee. *Ortho*-substituted aromatic aldehydes were next screened. Halide substituents were found compatible with the established conditions, although a better ee was obtained with the less sterically demanding fluorine atom, leading to **3fl** in 87% ee. On the contrary, mesomeric electron-withdrawing groups such as cyanide or nitro resulted in lower ee's. Aldehydes substituted at the *meta* position by either halogens or trifluoromethyl groups resulted in excellent ee's, higher than 90% for **3fo-3fq**. Despite a significant drop of the ee to 61%, the reaction was compatible with an unprotected phenol function leading to

Table 1. Optimization of the Reaction^a

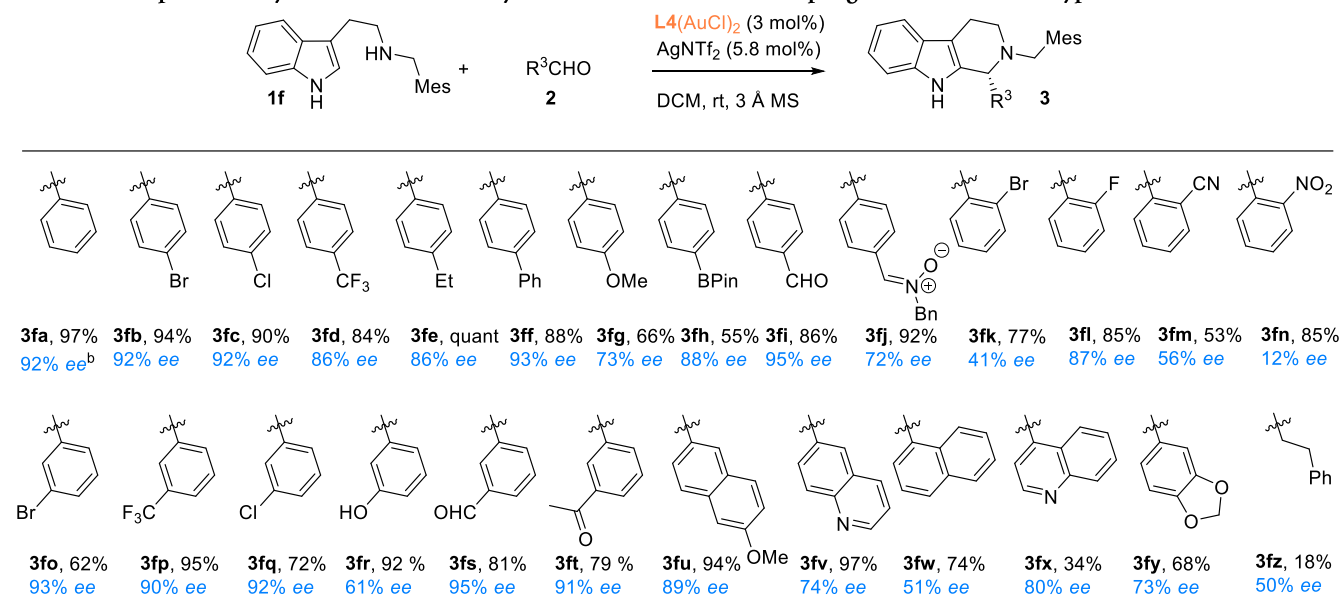
entry	1	catalyst	yield (%) ^b	ee ^c
1 ^d	1a	$Ph_3PAuNTf_2$ 4	3aa , 90	-
2	1a	$AgNTf_2$	3aa , 0	-
3	1a	$L_1(AuCl)_2$	3aa , 99	75
4	1b	$L_1(AuCl)_2$	3ba , 90	57
5	1c	$L_1(AuCl)_2$	3ca , 50	52
6	1d	$L_1(AuCl)_2$	3da , 88	74
7	1e	$L_1(AuCl)_2$	3ea , 80	75
8	1f	$L_1(AuCl)_2$	3fa , 84	83
9	1f	$L_2(AuCl)_2$	3fa , 82	91
10	1f	$L_3(AuCl)_2$	3fa , 32	80
11	1f	$L_4(AuCl)_2$	3fa , quant.	93
12	1f	$L_5(AuCl)_2$	3fa , 82	79
13	1f	$L_6(AuCl)_2$	3fa , 99	78



^a Reactions were run using **1** (0.1 mmol), **2a** (0.2 mmol) in DCM (1 mL) at rt. ^b Isolated yields. ^c Determined by chiral HPLC. ^d No silver salt added.

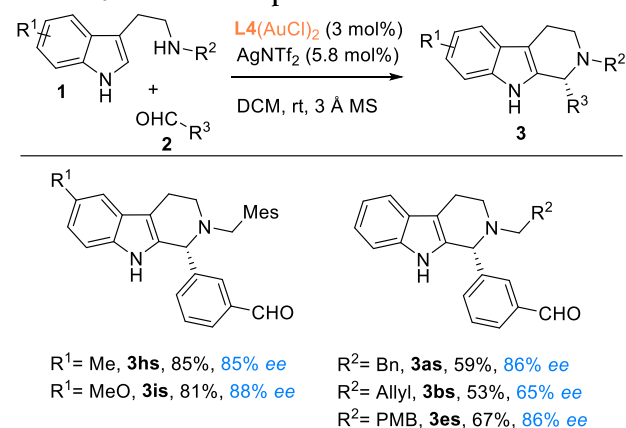
compound **3fr** in 92% yield. When the reaction was performed with a dialdehyde (*m*-phthalaldehyde **2s**), **3fs** was isolated in an excellent 95% ee with, again, no trace of difunctionalization. In a similar manner, with 3-acetylbenzaldehyde **2t**, the gold-catalyzed functionalization proved totally selective to the aldehyde over the ketone function. Bicyclic aldehydes were next screened and it was shown that 2-naphthaldehyde **2u** or 6-quinolinecarboxaldehyde **2v** were well tolerated, leading to 89 and 74% ee's, respectively. Compound **3fw** was obtained with a moderate 51% ee from 1-naphthaldehyde. Interestingly though, its aza-analogous 4-quinolinecarboxaldehyde **2x** led to **2fx** in a moderate 34% yield but with an excellent 80% ee. Finally, the piperonaldehyde led to **3fy** in 73% ee, introducing 1,3-benzodioxole scaffold present in numerous indolic drugs such as tadalafil.²³ Finally aliphatic aldehydes were screened, pointing out the limitation of this methodology to aromatic aldehydes. Indeed, with 3-phenylpropanal **2z**, the corresponding tetrahydro- β -carboline **3fz** was obtained in a low 18% yield and 50% ee. Other tryptamines bearing either a substituent on the indole ring or another group on the nitrogen were next used under the optimized conditions (Scheme 4). The reaction tolerated a methyl and a methoxy group at position 5 of the indole ring using **2s** as the aldehyde leading to **3hs** and **3js** with good enantioselectivities.

Scheme 3. Scope of Aldehydes in the Gold-Catalyzed Enantioselective Pictet-Spengler Reaction with Tryptamine 1f



^a Reactions were run using **1f** (0.3 mmol), **2** (0.6 mmol), powdered activated 3 Å molecular sieves (300 mg) in DCM (3 mL) at rt. ^b The product **3fa** was obtained in 89% yield and 83% ee when the reaction was performed at a 1 mmol scale of tryptamine **1f**.

Scheme 4. Additional Scope

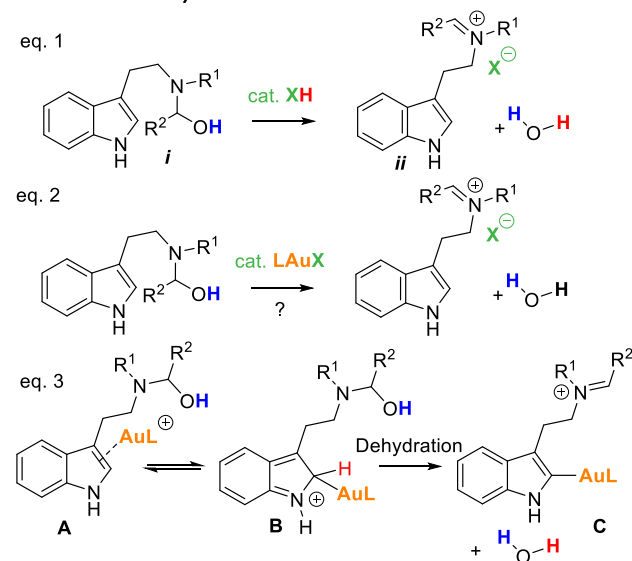


When the reaction was performed from *N*-benzyltryptamine **3a**, the product **3as** was obtained in an excellent 86% ee which dropped to 65% ee using an allyl group. A *p*-methoxy substituent proved very similar to a benzyl group, leading to **3es** in 86% ee and 67% yield.

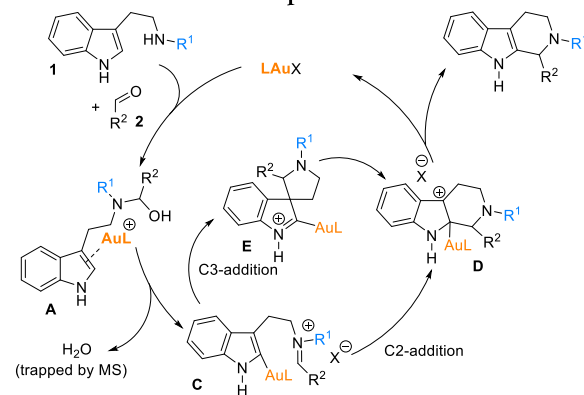
The mechanism of the Pictet-Spengler reaction is controversial about the nature of the addition of the indole ring to the iminium **ii** (Scheme 5).²⁴ However, regardless of the exact mechanism for the cyclization, all known Pictet-Spengler reactions undergo initially the formation of an iminium **ii** from a hemiaminal **i** and a protic catalyst, this step generating water (Scheme 5, eq. 1). The mechanistic issue associated with the Au(I)-catalyzed version of this reaction stands in (1) the questionable formation of the iminium and water while the reaction is seemingly performed in the absence of protons and the role of the Au(I) complex during this step (Scheme 5, eq. 2) and (2) the nature of the intermediates. Our hypothesis is that coordination of the π -Lewis acid Au(I) complex to the indole ring from **A** via C2 modifies the acidity of the proton at C2, thereby allowing an intramolecular dehydration from intermediate **B** to **C** (Scheme 5, eq. 3).^{25,26} However very little is known about the actual auration of indoles, most of the examples being extremely specific.^{27,28} The catalytic cycle would then consist in the formation of the key iminium **C** from the tryptamine **1**, aldehyde **2** and the gold catalyst through intermediate **A**. The addition of the indole ring to the iminium would

occur via the direct addition of C2 to lead to **D** (or alternatively, the C3 addition). After a deauration step regenerating the catalytic species, the product would be obtained (Scheme 6).

Scheme 5. Putative and Proposed Mechanistic Steps for the Formation of the Key Iminium



Scheme 6. Mechanistic Proposal



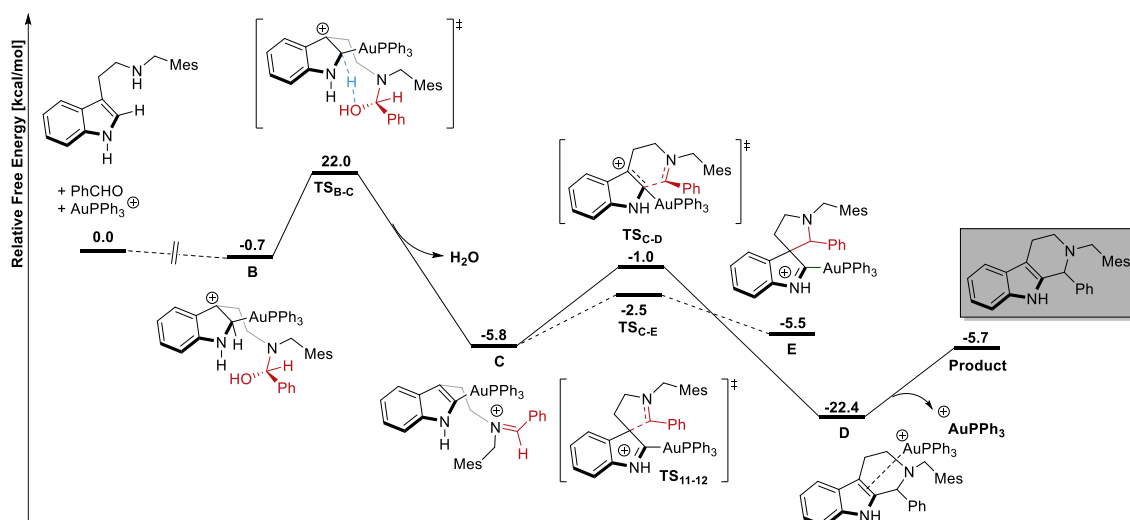


Figure 1. Computed Dehydration Pathway and Final Steps to the Product

The Au(I)-catalyzed Pictet-Spengler reaction of tryptamine **1f** with benzaldehyde using AuPPh_3^+ as model catalyst was studied by means of DFT computations (see the Supporting Information for details and additional computations). The investigations started by the computational analysis of the initial steps of the reaction from the hemiaminal **B**. Here, we focus on the process of dehydration and the formation of the final product. Figure 1 shows the results obtained on the computed mechanism that was postulated in Scheme 6. All energies are Gibbs free energy at 298 K including solvent correction for dichloromethane. The hemiaminal complex **B**, located at -0.7 kcal/mol, displays the Au(I) fragment at the C2 position of the indole moiety. The dehydration process involving the C2-H bond to form iminium **C** requires 22.7 kcal/mol of free energy of activation, i.e. 22.0 kcal/mol from the reference system. Subsequently, intermediate **C** may form the spiro complex **E** via C3 attack to the iminium. This virtually thermoneutral spiroindolization requires only 3.3 kcal/mol of free energy of activation. It is thus easily reversible. Importantly, a C3 to C2 C-C bond migration that would form a 6-member ring **D** could not be modeled, which is consistent with previous observations in the field of organocatalyzed Pictet-Spengler reactions.²⁴ Alternatively, intermediate **C** can also be directly cyclized from the C2 position to give **D** at the expense of a moderate energy barrier of 4.8 kcal/mol. This step is appreciably exergonic by 16.6 kcal/mol. Finally, intermediate **D** releases the catalyst and the observed product, lying at -5.7 kcal/mol on the free energy surface.

In conclusion, we have developed a new route to chiral tetrahydro- β -carbolines with high enantioselectivities using Au(I) catalysis. Though limited to aromatic aldehydes, the reaction tolerates a large number of reactive functions with high chemoselectivity. The Au(I) complex serves as an activator by binding to the indole ring thereby allowing the formation of the key iminium with concomitant metalation at C2 of the indole ring. It is to bet that this new reactivity will pave the way to new strategies in the growing field of gold catalysis applied to heterocyclic chemistry.

ASSOCIATED CONTENT

Supporting Information

Details of the experimental procedures, NMR spectra, HPLC, spectroscopical and computational data. The Supporting Information is available free of charge on the ACS Publications website.

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25. A and B might well be resonance structures.

26. With the natural high nucleophilicity of the indole ring at C3, another hypothesis through the auration at C3 of the indole has been considered and is presented in the Supporting Information.

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